REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60
(Large Entity)

DOCKET NUMBER	ANTICIPATED CLASSIFICATION OF THIS APPLICATION		PRIOR APPLICATION	ART UNIT
	CLASS	SUBCLASS		
SALK1280-4			08/695,743	

Address to:
Assistant Commissioner for Patents
Washington, D.C. 20231

This is a request for filing a ☐ continuation ☒ divisional application under 37 CFR 1.60 of pending prior application, Serial Number 08/695,743 filed on August 12, 1996 and entitled:
USE OF SELECTIVE LIGANDS FOR TREATMENT OF DISEASE STATES RESPONSIVE TO STEROID OR STEROID-LIKE RETINOIDS

1. Enclosed is a copy of the latest inventor-signed prior application, including a copy of the oath or declaration showing the original signature or an indication it was signed. I hereby verify that the attached papers are a true copy of the latest signed prior application, Serial Number 08/193,146 , and further that all statements made herein of my own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like are made punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	15	- 20 =	0	x	$22.00	$0.00
Indep. Claims	2	- 3 =	0	x	$80.00	$0.00
Multiple Dependent Claims (check if applicable)		☐				$0.00
					BASIC FEE	$770.00
					TOTAL FILING FEE	$770.00

2. ☒ The Commissioner is hereby authorized to charge any fees which may be required under 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. 07-1895 A duplicate copy of this sheet is enclosed.

3. ☐ A check in the amount of _____ is enclosed.

4. ☐ Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

5. ☒ Amend the specification by inserting before the first line the sentence: "This application is a ☐ continuation ☒ division of application Serial Number 08/695,743 filed August 12, 1996 which application is now:
   - ☐ abandoned.
   - ☒ pending, and
   - ☒ other (explain): which is a continuation of USSN 08/193,146, filed 02/14/94, now abandoned, which claims priority from PCT US92/07064, which is a continuation-in-part of USSN 07/748,767, filed 08/23/91, now abandoned.

6. ☐ Transfer the drawings from the pending prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application. (May only be used if signed by person authorized by 37 CFR 1.138 and before payment of issue fee.)

REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60
(Large Entity)

7. ☐ New formal drawings are enclosed.

8. ☐ Priority of foreign application number _____ filed on _____ in _____ (Country) is claimed under 35 U S C 119

☐ The certified copy has been filed in prior application Serial Number _____ filed on _____

9. ☐ A preliminary amendment is enclosed.

10. ☒ The prior application is assigned of record to
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

11 ☒ The inventor(s) of the invention being claimed in this application is (are):
Ronald M. Evans
Richard A. Heyman
Christina S. Berger
Robert B. Stein

12. ☒ The power of attorney in the prior application is to

Stephen E. Reiter, Registration No. 31,192

a ☐ The power of attorney appears in the original papers in the prior application

b ☒ Since the power of attorney does not appear in the original papers, copies of the power of attorney in the prior application is enclosed.

c ☒ Address all future correspondence to (May only be completed by applicant, or attorney or agent of record.)

Stephen E. Reiter
GRAY CARY WARE & FREIDENRICH
4365 Executive Drive, Suite 1600
San Diego, CA 92121-2189

Dated: September 16 1997

_____
Signature

Stephen E. Reiter
Typed or printed name

31,192
Registration Number (if applicable)

☐ Inventor(s)

☐ Assignee of complete interest

☒ Attorney or agent of record

☐ Filed under 37 C.F.R. 1.34(a)

cc:

USE OF SELECTIVE LIGANDS FOR TREATMENT OF DISEASE STATES RESPONSIVE TO STEROID OR STEROID-LIKE HORMONES

RELATED APPLICATIONS

This application is a continuation-in-part of United States Application Serial No. 07/748,767, filed August 23, 1991, now pending.

FIELD OF THE INVENTION

The present invention relates to therapeutic uses of compounds which function as steroid hormones or steroid-like hormones. In a particular aspect, the present invention relates to the use of compounds which selectively or preferentially interact with a single subtype of a given steroid hormone or steroid-like hormone receptor class.

BACKGROUND OF THE INVENTION

Many disease states are consistently associated with the occurrence of karyotypic change, e.g., a chromosomal translocation. For example, when the gene encoding PML (for "promyelocytes") undergoes a translocation with the retinoic acid receptor-α (RAR-α) (i.e., translocation between chromosomes 15 and 17 at the RAR-α and PML loci), the translocation is manifested as a form of leukemia, acute promyelocytic leukemia (APL).

It is possible, and even likely in many cases, that when translocation occurs, a gene product not normally subject to hormone expression control (e.g., PML) may be placed under the control of a hormone responsive sequence (e.g., RAR-α). Thus a gene such as PML may fall under the control of a hormone responsive sequence (such as RAR-α) as a result of a translocation event.

It has recently been discovered that APL can be effectively controlled by treatment with retinoic acid. Unfortunately, since several different receptors (and subtypes thereof) are known which respond to retinoic acid (e.g., RAR-α, RAR-ß, RAR-γ, RXR-α, RXR-ß, RXR-γ), administration of retinoic acid as a treatment for APL has the potential to cause many undesirable side-reactions for the patient.

There are numerous other disease states which have also been found to be responsive to treatment with hormones and/or hormone-like compounds. For example, Vitamin D-dependent Ricketts is responsive to treatment with Vitamin D, acne is responsive to treatment with retinoic acid, and the like. While available hormone or hormone-like compounds are effective for the treatment of such disease states, there is always the competing concern of undesirable side effects of such hormone treatments.

Accordingly, such disease states can potentially be much more effectively treated by using ligands which are selective for the specific receptor subtype which is involved in the disease state. Indeed, in view of the potential for the use of hormone therapy in the treatment of many disease states, it would be desirable to have the ability to selectively treat subjects with compounds which selectively interact as ligands with the specific receptor subtype involved in the disease state.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, we have discovered various compounds which selectively interact with a single receptor subtype, to a much greater extent than than do other subtypes of the same receptor class.

Such compounds are useful for the selective treatment of hormone responsive disease states, thereby minimizing the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a dose response curve showing the response of RAR-α, RAR-ß, RAR-γ, and RXR-α to increasing concentrations of retinoic acid.

Figure 2 is a dose response curve showing the response of RAR-α, RAR-ß, RAR-γ, and RXR-α to increasing concentrations of the phenyl-naphthyl derivative referred to herein as Compound I.

Figure 3 is a dose response curve showing the response of RAR-α, RAR-ß, RAR-γ, and RXR-α to increasing concentrations of the polyunsaturated carboxylic acid derivative referred to herein as Compound II.

Figure 4 is a dose response curve showing the response of RAR-α, RAR-ß, RAR-γ, and RXR-α to increasing concentrations of the amide derivative referred to herein as Compound III.

Figure 5 is a dose response curve showing the response of RAR-α, RAR-ß, RAR-γ, and RXR-α to increasing concentrations of the benzophenone derivative referred to herein as Compound IV.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided methods for the treatment of a subject afflicted with a steroid or steroid-like hormone-responsive

disease state, said method comprising administering to said subject an effective amount of a ligand which selectively interacts with the steroid or steroid-like hormone receptor subtype associated with said steroid or steroid-like hormone-responsive disease state, wherein said ligand selectively interacts with said steroid or steroid-like hormone receptor subtype associated with said steroid or steroid-like hormone-responsive disease state, to a significantly greater extent than do other subtypes of the same receptor class.

As employed herein, the phrase "steroid or steroid-like hormone-responsive disease state" refers to:

(i) any disease state wherein a gene product (or a portion of a gene product) not normally subject to steroid or steroid-like hormone expression control is placed, by translocation, under the control of a steroid or steroid-like hormone responsive sequence, or

(ii) any disease state wherein a first gene product (or a portion of a gene product) subject to steroid or steroid-like hormone expression control by a first steroid or steroid-like hormone is placed, by translocation, under the control of a second steroid or steroid-like hormone responsive sequence, or

(iii) any disease state which correlates with the expression of abnormal gene product, wherein said gene product (or a portion of said gene product) is normally subject to steroid or steroid-like hormone expression control, or

(iv) any disease state which correlates with an abnormal level of expression of gene product, the expression of which is normally maintained under steroid or steroid-like hormone expression control, or

(v) any disease state which correlates with an abnormal level of receptor, the presence of which is normally maintained under steroid or steroid-like hormone expression control, or

(vi) any disease state which correlates with an abnormal level of ligand, the presence of which is normally maintained under steroid or steroid-like hormone expression control.

As employed herein, the phrase "ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state to a significantly greater extent than with other subtypes of the same receptor class" refers to compounds which are preferentially selective for one receptor subtype in modulating the transcription activation properties thereof. The terminology "significantly greater extent", as applied to interaction between ligand and a specific receptor subtype, refers to ligands which have a significantly higher therapeutic index (i.e., the ratio of efficacy to toxicity) for treatment of the target disease state than for activation of pathways mediated by other subtypes of the same receptor class. The toxicity of therapeutic compounds frequently arises from the non-selective interaction of the therapeutic compound with receptor subtypes other than the desired receptor subtype. Thus, the present invention provides a means to dramatically reduce the incidence of side-reactions commonly associated with hormone therapy. See, for example, the selectivity demonstrated in Figures 2-5.

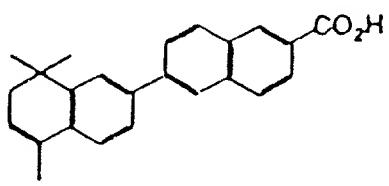
It is useful to distinguish the terms receptor "subtype" and receptor "class". For example, retinoid responsive receptors comprise a "class" of receptors, all of which are responsive to retinoid compounds. Similarly, thyroid hormone receptors comprise a "class" of receptors which are responsive to thyroid hormone. Each class can be

divided into various subtypes, i.e., specific members of the class which have different tissue distributions, different affinities for the native ligand, different activation properties when contacted with the native ligand, and so on.

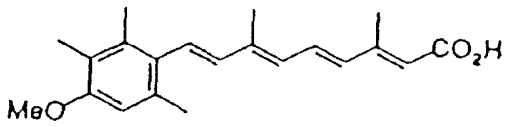
Some classes of receptors include sub-families of distinctly different types of receptors. Thus, for example, while the retinoid class of receptors includes both the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), these two different sub-families are clearly distinct. For example, each member of the RAR sub-family is responsive to a defined first hormone response element (HRE), and each member of the RXR sub-family is responsive to a defined second HRE (which is distinctly different from the first HRE). Accordingly, in accordance with the present invention, there are provided compounds which distinguish between the various sub-families of a receptor, and/or distinguish between the various subtypes thereof.

Ligands contemplated by the present invention are selected from RAR-α selective ligands, RAR-ß selective ligands, RAR-γ selective ligands, TR-α-selective ligands, TR-ß-selective ligands, RXR-α selective ligands, RXR-ß selective ligands, RXR-γ selective ligands, coup-α selective ligands, coup-ß selective ligands, coup-γ selective ligands, and the like.

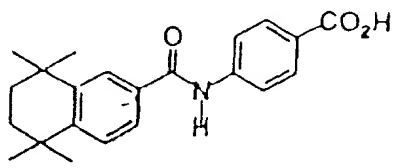
Exemplary selective ligands contemplated for use in the practice of the present invention include the phenyl-naphthyl derivative having the structure:



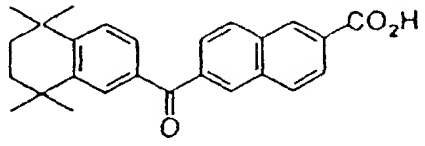
referred to herein as Compound I, which selectively interacts with the retinoic acid receptor-ß and retinoic acid receptor-γ (see, for example, FIG. 2); the polyunsaturated carboxylic acid derivative having the structure:



referred to herein as Compound II, which selectively interacts with RAR subtypes relative to RXR subtypes (see, for example, FIG. 3); the amide having the structure:



referred to herein as Compound III, which selectively interacts with RAR-α, and displays a different rank order of potency relative to the other RAR subtypes and RXR-α, relative to the other retinoid compounds tested (see, for example, FIG. 4); the benzophenone derivative having the structure:



referred to herein as Compound IV, which selectively interacts with the retinoic acid receptor-ß and retinoic acid receptor-α (see, for example, FIG. 5), and the like. These and many other compounds useful in the practice of the present invention are described in detail in Chemistry and Biology of Synthetic Retinoids, Dawson and Okamura,

editors, CRC Press, Inc. (Boca Raton, FL 1990), incorporated by reference herein.

The above-described ligands, in suitable form (employing suitable vehicle for delivery, such as, for example, gelatin capsule(s) or compressed tablet(s) where oral administration is contemplated; in an appropriate base where topical administration is contemplated; in a suitable infusion medium where injection or other means of delivery are contemplated; and the like), can be administered to a subject employing standard methods, such as, for example, orally, topically (e.g., transdermal mode of administration), by intraperitoneal, intramuscular, intravenous, or subcutaneous injection or implant, and the like. One of skill in the art can readily determine appropriate dosage(s), treatment regimens, etc. depending on the mode of administration employed.

For example, for oral administration, dosages in the range of about 1 up to 500 mg/kg body weight per day, depending on the disease state being treated, will be employed. Active compound can be administered in a sustained release form, or in divided doses throughout the day. For topical delivery, in the range of about 0.05 mg up to 10 mg/kg body weight per day, depending on the disease state being treated, will be employed. For injection modes of delivery, in the range of about 10 μg up to 2 mg/kg body weight per day, depending on the disease state being treated, will be employed. It should be emphasized, however, that dosage requirements are variable and are typically individualized on the basis of the disease under treatment and the response of the patient. After a favorable response is noted, the proper maintenance dosage can be determined by decreasing the initial drug dosage in small increments at appropriate time intervals until the lowest drug dosage which will maintain an adequate clinical response is reached. Those of skill in

the art recognize that constant monitoring of the patient's condition is desirable in regards to drug dosage.

In accordance with a particular embodiment of the present invention, there is provided a method for the treatment of a subject afflicted with acute promyelocytic leukemia, said method comprising administering to said subject an effective amount of a ligand which selectively interacts with retinoic acid receptors, in preference to retinoid X receptors. In a preferred embodiment of the present invention, an effective amount of a ligand which selectively interacts with RAR-α, relative to other retinoic acid receptor subtypes (as well as retinoid X receptors), will be employed. Ultimately, physicians will determine the particular dosage of the selective ligand which is most suitable. The selected dosage will vary depending upon the mode of administration employed, the particular compound administered, the patient under treatment, and the particular disease being treated.

In addition to the above-described applications of the invention treatment method, the method of the invention can be applied to the selective treatment of skin disorders such as acne, psoriasis, photodamage, and the like. For such applications, compounds which selectively interact with RAR-α, relative to other retinoid receptors, are preferred.

It can be readily seen, therefore, that the invention treatment method is useful in the treatment of a wide variety of disease states.

The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLES

A series of dose response curves were generated to determine the response of retinoic acid receptor-α, retinoic acid receptor-β, retinoic acid receptor-γ and retinoid X receptor-α upon exposure to retinoic acid, Compound I (i.e., the phenyl-naphthyl derivative), Compound II (i.e., the polyunsaturated carboxylic acid derivative), and Compound III (i.e., the amide derivative), and Compound IV (i.e., the benzophenone derivative).

Response to the various compounds was measured employing the "cis/trans assay" as described by Evans et al., in USSN 108,471 (filed November 30, 1988), the entire contents of which are hereby incorporated by reference herein. All assays were carried out employing CV-1 host cells co-transformed with vectors encoding a receptor selected from RAR-α, RAR-β, RAR-γ, or RXR-α and a reporter vector.

The retinoic acid receptor-α was encoded by vector pRShRAR-alpha (see US Patent No. 4,981,784, issued January 1, 1991, the entire contents of which are hereby incorporated by reference herein), retinoic acid receptor-β was encoded by vector pRShRAR-beta (see Brand et al. in Nature 332:850 (1988) and Benbrook et al. in Nature 333:669 (1988), the entire contents of which are hereby incorporated by reference herein), retinoic acid receptor-γ was encoded by vector pRShRAR-gamma (see USSN 370,407, filed June 22, 1989, the entire contents of which are hereby incorporated by reference herein), and retinoid X receptor-α was encoded by vector pRShRXR-alpha (see USSN 478,071, filed February 9, 1990, the entire contents of which are hereby incorporated by reference herein).

The reporter vector used in all experiments was TREp-ΔMTV-LUC, as described by Umesono et al. in Nature 336:262 (1988), the entire contents of which are hereby incorporated by reference herein.

EXAMPLE I

RETINOIC ACID DOSE RESPONSE CURVE

Figure 1 presents the results of a dose response study carried out with retinoic acid as the ligand for each of the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

At very low concentrations of retinoic acid (i.e., concentrations below about $1x10^{-9}$), each of the retinoid receptor subtypes is activated to approximately the same extent. Similarly, at concentrations above about $1x10^{-6}$, each of the retinoid receptor subtypes is activated to approximately the same extent. Although, in the concentration range of about $1x10^{-9}$ - $1x10^{-6}$, there is a readily discerned rank order potency as follows:

$$\text{RAR-}\gamma > \text{RAR-}\beta > \text{RAR-}\alpha > \text{RXR-}\alpha,$$

retinoic acid is seen to exert a substantial effect on each of the retinoid receptors tested. Administration of retinoic acid as a therapeutic agent is, therefore, likely to induce many hormone mediated pathways, not just the pathway involved in the disease state to be treated.

EXAMPLE II

DOSE RESPONSE CURVE FOR COMPOUND I

Figure 2 presents the results of a dose response study carried out with Compound I (phenyl-naphthyl derivative) as the ligand for each of the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

At very low concentrations of Compound I (i.e., concentrations below about $1x10^{-8}$), each of the retinoid receptor subtypes is activated to approximately the same extent. However, at concentrations above about $1x10^{-8}$, there is a readily discerned rank order potency as follows:

$$RAR\text{-}\gamma \approx RAR\text{-}\beta >>> RAR\text{-}\alpha \approx RXR\text{-}\alpha.$$

Thus, Compound I could be used for the treatment of a disease state which involves RAR-γ and/or RAR-β, without perturbing pathways which are responsive to RAR-α or the retinoid X receptor.

EXAMPLE III

DOSE RESPONSE CURVE FOR COMPOUND II

Figure 3 presents the results of a dose response study carried out with Compound II (polyunsaturated carboxylic acid derivative) as the ligand for each of the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

At very low concentrations of Compound II (i.e., concentrations below about $1x10^{-9}$), each of the receptor subtypes is activated to approximately the same extent. However, at concentrations above about $1x10^{-8}$, the rank order potency is as follows:

$$RAR\text{-}\gamma \approx RAR\text{-}\beta \approx RAR\text{-}\alpha >> RXR\text{-}\alpha.$$

Thus, Compound II could be used for the treatment of a disease state which involves a retinoic acid receptor, without perturbing pathways which are responsive to the retinoid X receptor.

EXAMPLE IV

DOSE RESPONSE CURVE FOR COMPOUND III

Figure 4 presents the results of a dose response study carried out with Compound III (amide derivative) as the ligand for each of the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

At very low concentrations of Compound III (i.e., concentrations below about $1x10^{-9}$), each of the receptor subtypes is activated to approximately the same extent. Similarly, at concentrations above about $1x10^{-7}$, each of the receptor subtypes is activated to approximately the same extent. However, at concentrations between about $1x10^{-9}$ and $1x10^{-7}$, the rank order potency is as follows:

$$RAR\text{-}\alpha > RAR\text{-}\beta \approx RXR\text{-}\alpha > RAR\text{-}\gamma.$$

Thus, Compound III could be used for the treatment of a disease state which involves RAR-α, while perturbing pathways which are responsive to other retinoid receptors to a much lesser extent.

EXAMPLE V

DOSE RESPONSE CURVE FOR COMPOUND IV

Figure 5 presents the results of a dose response study carried out with compound IV (benzophenone derivative) as the ligand for each of the receptors: RAR-α, RAR-ß, RAR-γ, and RXR-α.

At very low concentrations of Compound IV (i.e., concentrations below about $1x10^{-9}$), each of the receptor subtypes is activated to approximately the same extent. However, at concentrations above about $1x10^{-8}$, there is a readily discernible rank order potency as follows:

RAR-$\gamma \approx$ RAR-β >>> RAR-$\alpha \approx$ RXR-α.

Thus, Compound IV could be used for the treatment of a disease state which involves RAR-γ and/or RAR-β, without perturbing pathways which are responsive to RAR-α or the retinoid X receptor.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A method for the treatment of a subject afflicted with a steroid or steroid-like hormone-responsive disease state, said method comprising administering to said subject an effective amount of a ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state, to a significantly greater extent than with other subtypes of the same receptor class.

2. A method according to claim 1 wherein said disease state is retinoid responsive.

3. A method according to claim 2 wherein said ligand is selective for retinoic acid receptor-mediated processes, relative to retinoid X mediated processes.

4. A method according to claim 2 wherein said ligand is selective for retinoid X receptor-mediated processes, relative to retinoic acid mediated processes.

5. A method according to Claim 1 wherein said steroid or steroid-like hormone responsive disease state is the result of translocation of a portion of a gene encoding a member of the steroid/thyroid superfamily of receptors and a portion of a second gene; wherein the expression of said second gene is not ordinarily subject to regulation by the steroid or steroid-like hormone which binds to said member of the steroid/thyroid superfamily of receptors.

6. A method according to Claim 5 wherein said steroid or steroid-like hormone-responsive disease state is APL.

7. A method according to Claim 1 wherein said steroid or steroid-like hormone-responsive disease state is a skin disorder.

8. A method according to Claim 1 wherein said ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state is selected from RAR-α selective ligands, RAR-ß selective ligands, RAR-γ selective ligands, TR-α-selective ligands, TR-ß-selective ligands, RXR-α selective ligands, RXR-ß selective ligands, RXR-γ selective ligands, coup-α selective ligands, coup-ß selective ligands, or coup-γ selective ligands.

9. A method according to Claim 8 wherein said RAR-α selective ligand is the amide Compound III.

10. A method according to Claim 8 wherein said RAR-ß selective ligand is the phenyl-naphthyl derivative Compound I or benzophenone derivative Compound IV.

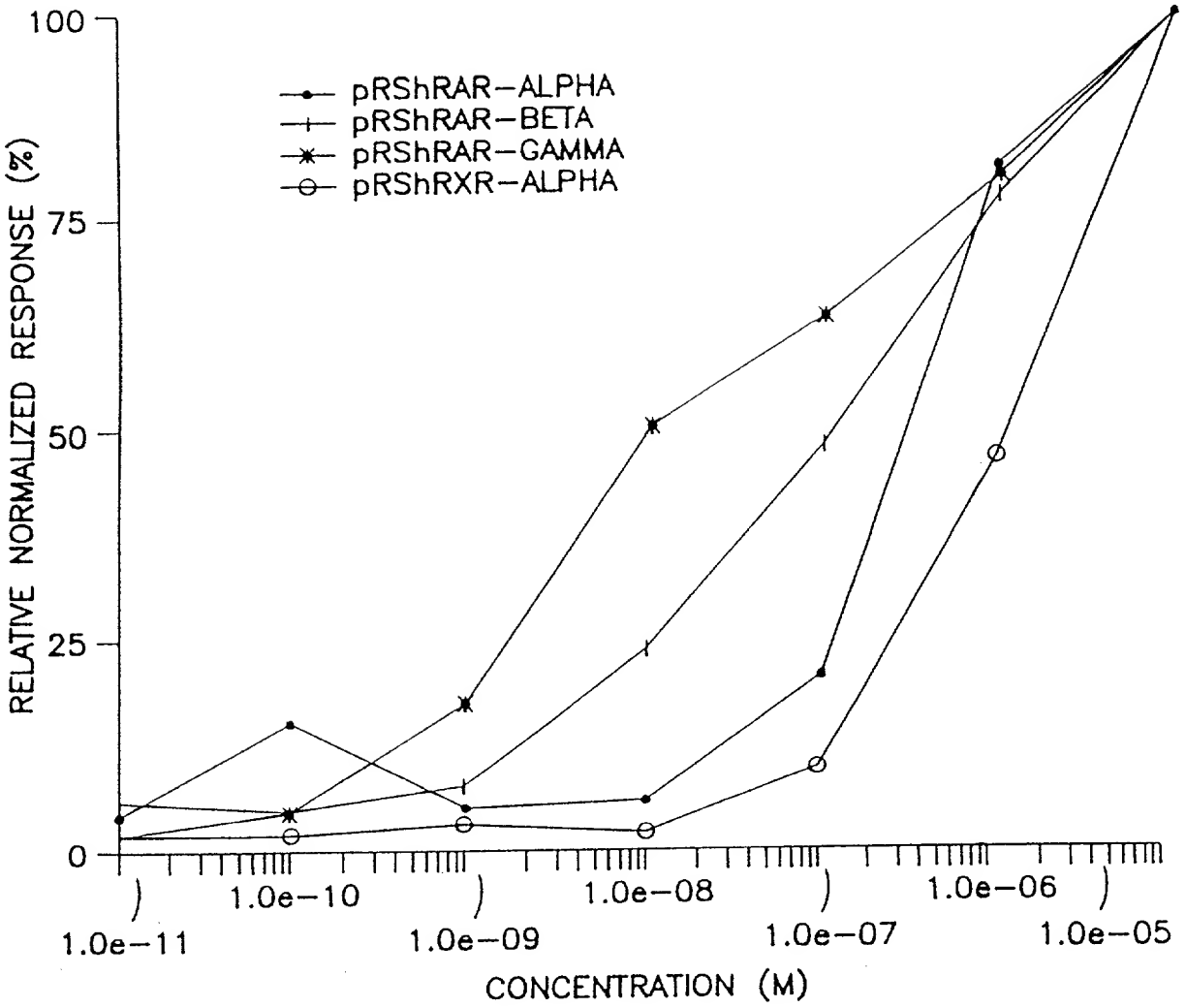
11. A method according to Claim 8 wherein said RAR-γ selective ligand is the phenyl-naphthyl derivative Compound I or benzophenone derivative Compound IV.

12. A method for the treatment of a subject afflicted with acute promyelocytic leukemia, said method comprising administering to said subject an effective amount of a ligand which selectively interacts with retinoic acid receptors, in preference to retinoid X receptors.

13. A method according to Claim 12 wherein said ligand selectively interacts with RAR-α, relative to other retinoic acid receptor subtypes, including retinoid X receptors.

14. A method according to Claim 12 wherein said ligand which selectively interacts with retinoic acid receptors, relative to retinoid X receptors, is the polyunsaturated carboxylic acid derivative Compound II.

15. A method according to Claim 13 wherein said ligand which selectively interacts with RAR-α is the amide Compound III.


100
75
50
25
0
RELATIVE NORMALIZED RESPONSE (%)
pRShRAR–ALPHA
pRShRAR–BETA
pRShRAR–GAMMA
pRShRXR–ALPHA
1.0e–11
1.0e–10
1.0e–09
1.0e–08
1.0e–07
1.0e–06
1.0e–05
CONCENTRATION (M)

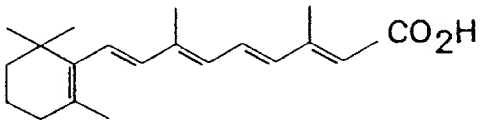
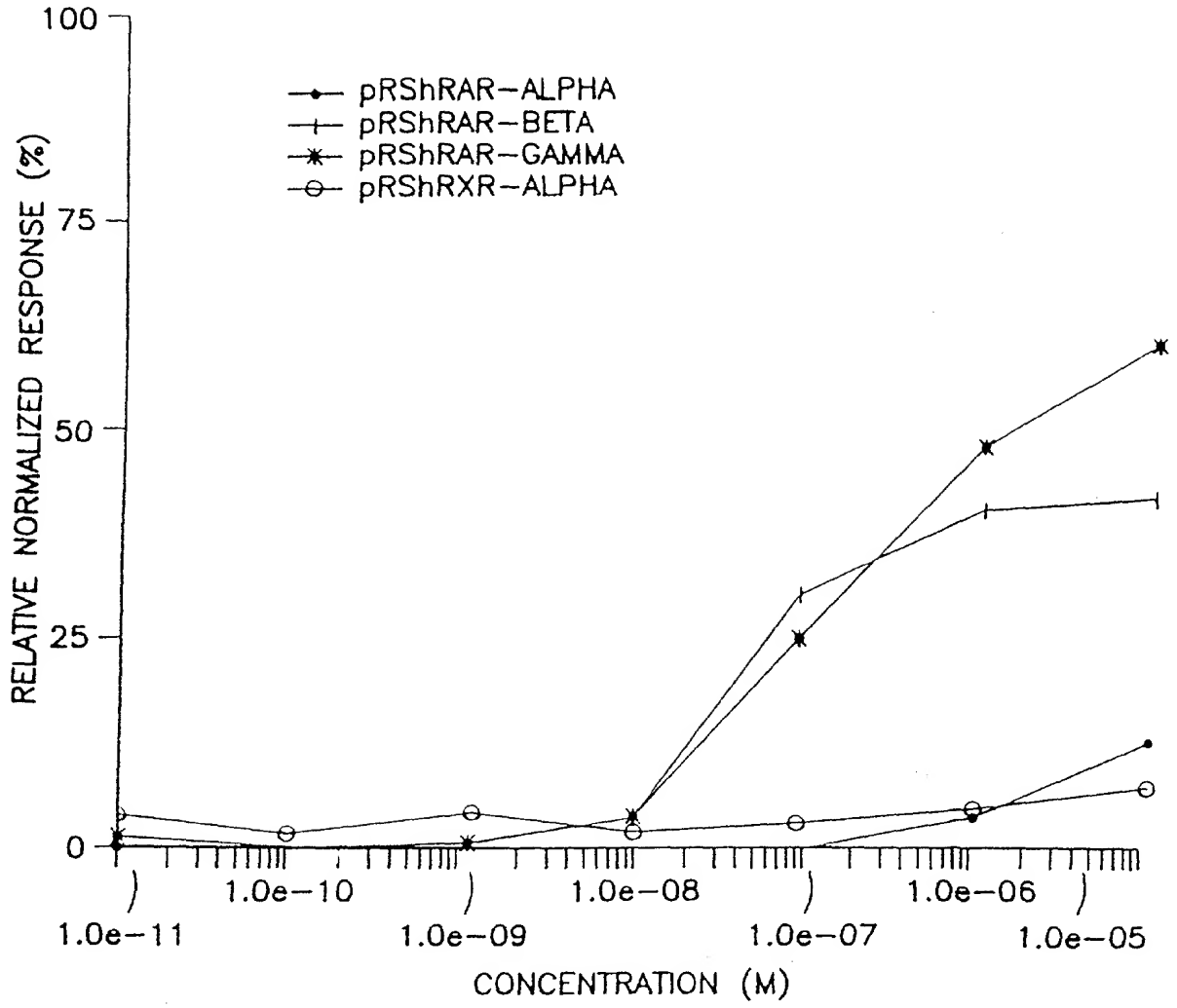

CO2H

FIG. 1


100
75
50
25
0
RELATIVE NORMALIZED RESPONSE (%)
pRShRAR-ALPHA
pRShRAR-BETA
pRShRAR-GAMMA
pRShRXR-ALPHA
1.0e-11
1.0e-10
1.0e-09
1.0e-08
1.0e-07
1.0e-06
1.0e-05
CONCENTRATION (M)

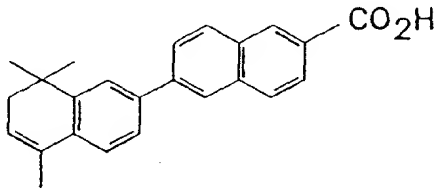
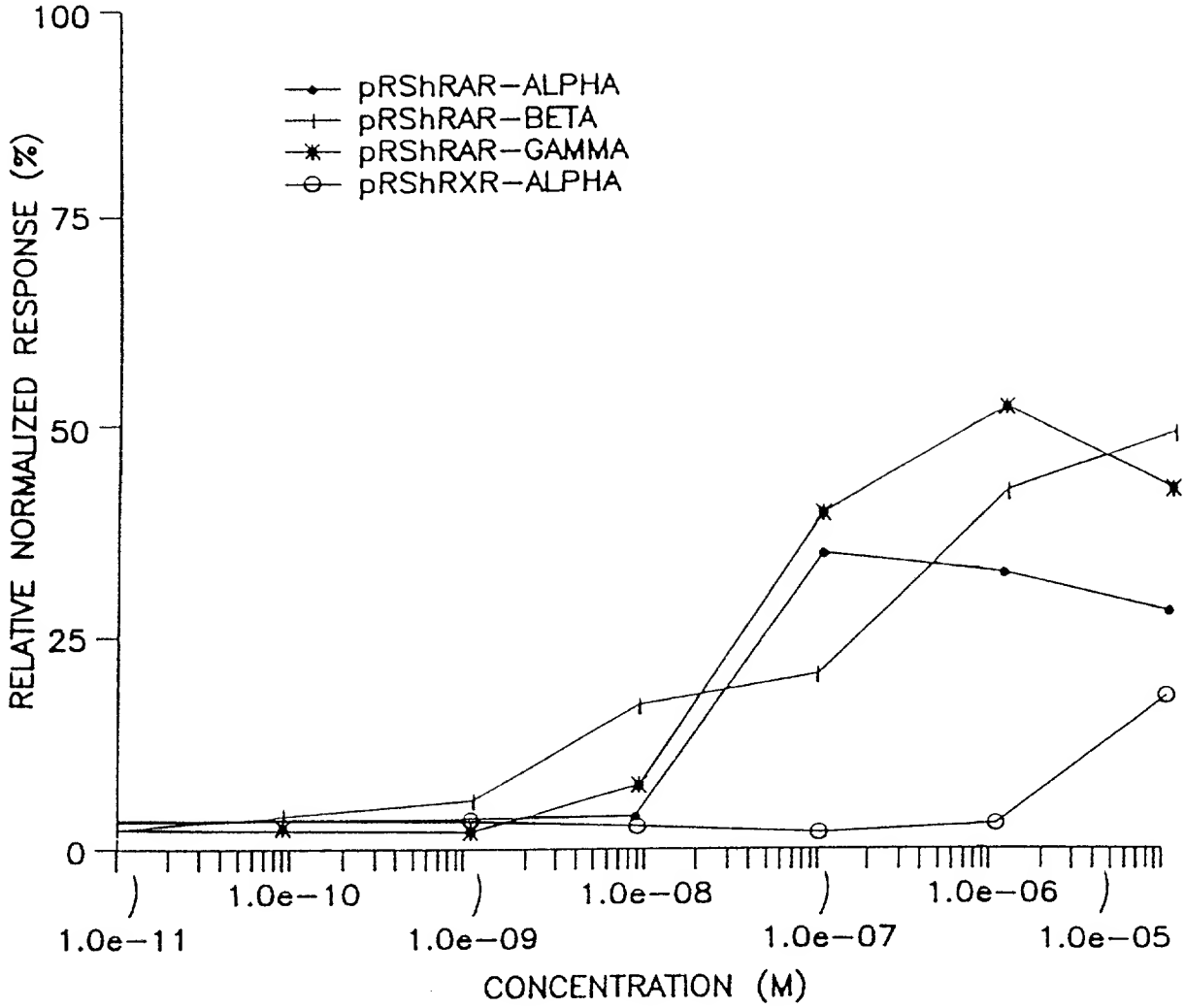

CO2H

FIG. 2


100
75
50
25
0
RELATIVE NORMALIZED RESPONSE (%)
pRShRAR–ALPHA
pRShRAR–BETA
pRShRAR–GAMMA
pRShRXR–ALPHA
1.0e–11
1.0e–10
1.0e–09
1.0e–08
1.0e–07
1.0e–06
1.0e–05
CONCENTRATION (M)

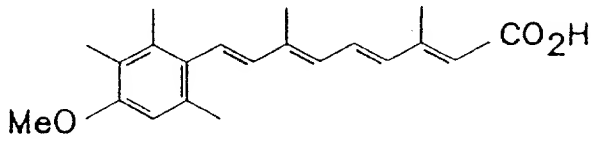
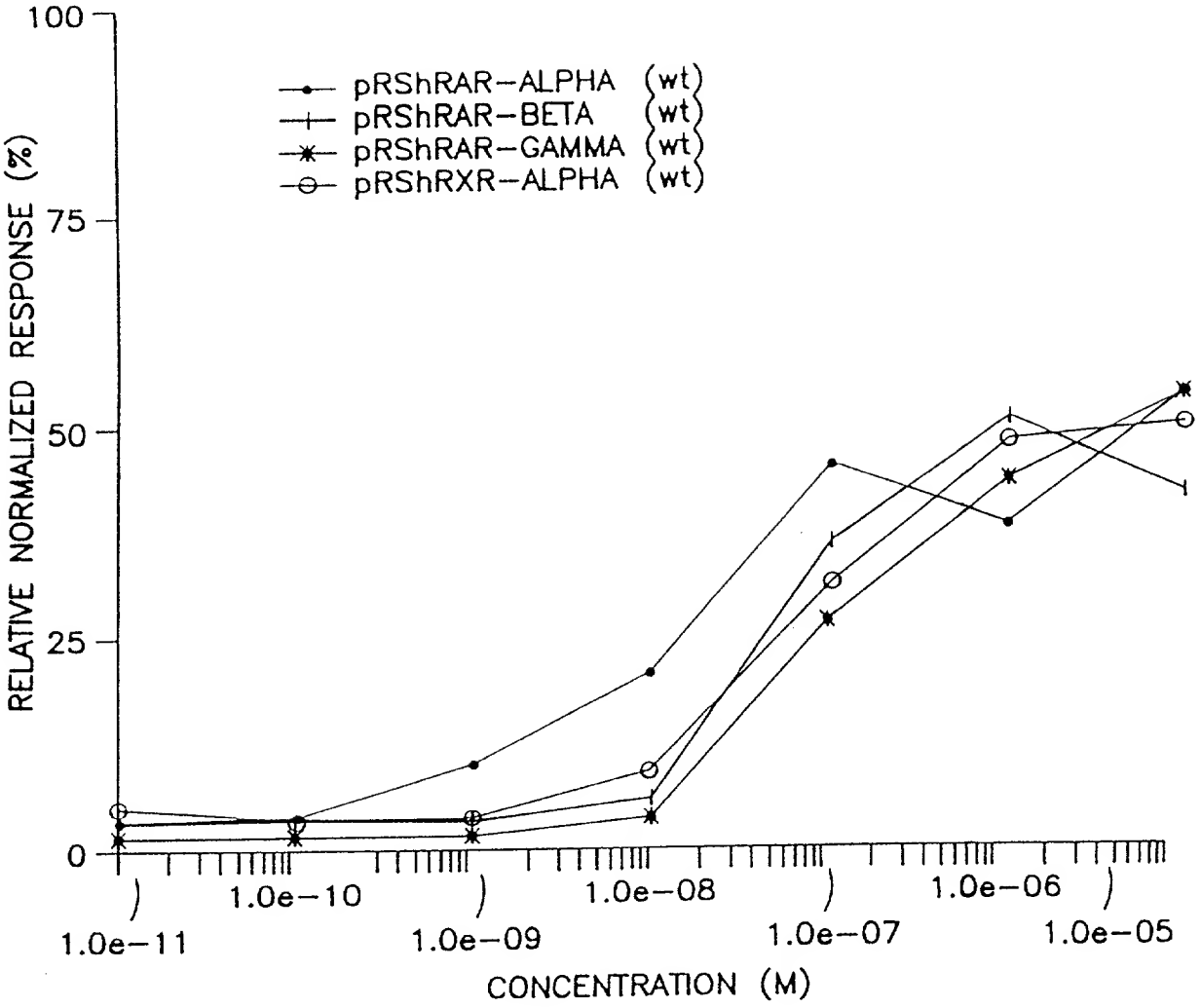

CO2H
MeO

FIG. 3


100
75
50
25
0
RELATIVE NORMALIZED RESPONSE (%)
pRShRAR–ALPHA (wt)
pRShRAR–BETA (wt)
pRShRAR–GAMMA (wt)
pRShRXR–ALPHA (wt)
1.0e–11
1.0e–10
1.0e–09
1.0e–08
1.0e–07
1.0e–06
1.0e–05
CONCENTRATION (M)

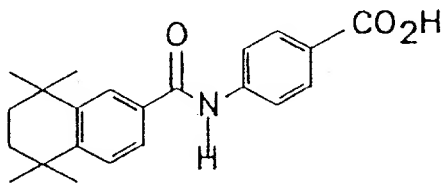
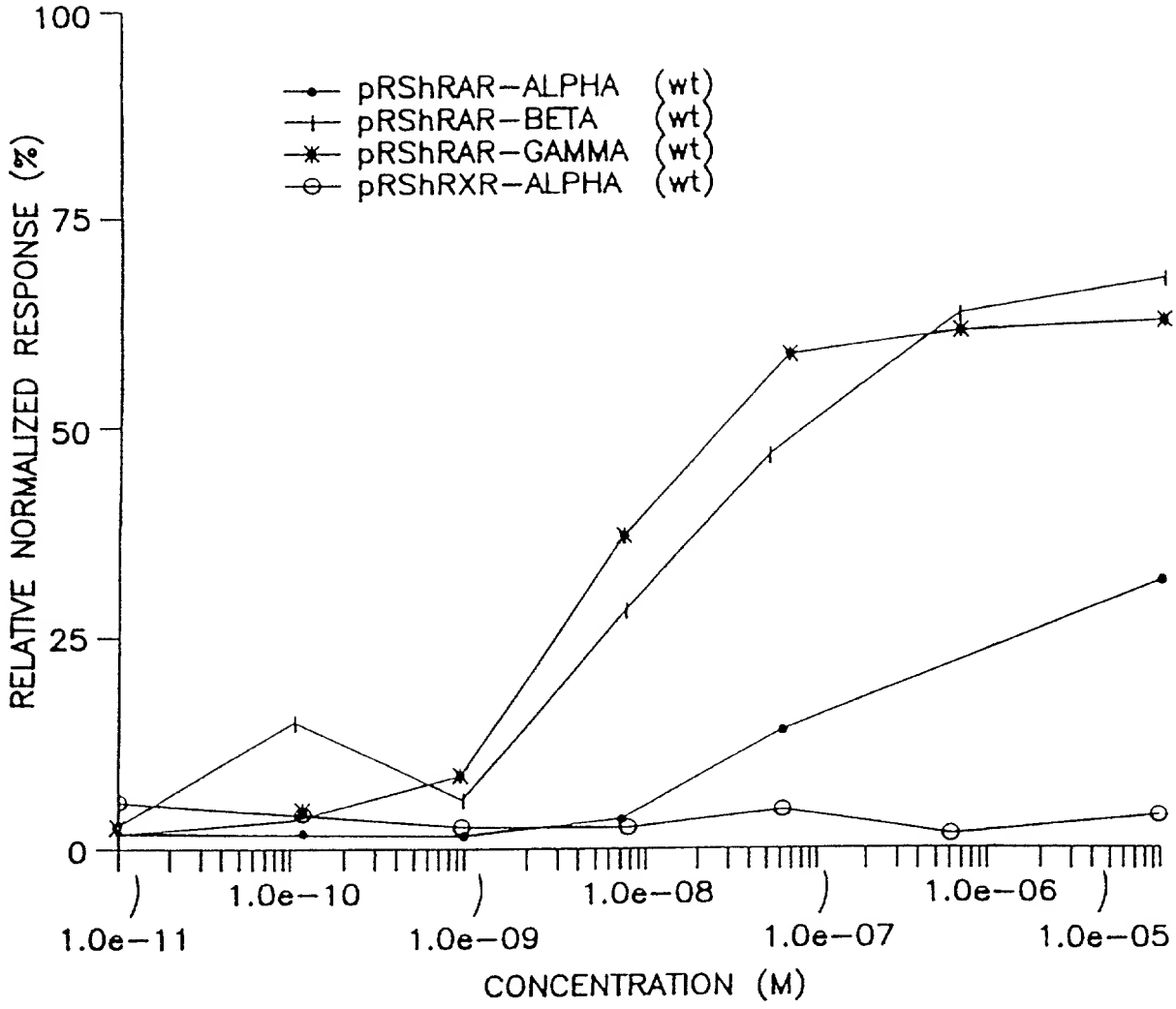

O
N
H
CO2H

FIG. 4


100
75
50
25
0
RELATIVE NORMALIZED RESPONSE (%)
pRShRAR–ALPHA (wt)
pRShRAR–BETA (wt)
pRShRAR–GAMMA (wt)
pRShRXR–ALPHA (wt)
1.0e–11
1.0e–10
1.0e–09
1.0e–08
1.0e–07
1.0e–06
1.0e–05
CONCENTRATION (M)

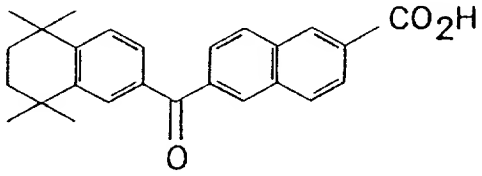

CO2H
O

FIG. 5

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/US92/07064

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 1-15 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ANIMAL BODY, THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see attached sheet .../...

3. [ ] Claims Nos..
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	J.E.F. REYNOLDS 'MARTINDALE THE EXTRA PHARMACOPOEIA' 1989 , THE PHARMACEUTICAL PRESS , LONDON Acitretin see page 916	1,2,7
X	EP,A,0 220 118 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES) 29 April 1987	1,2,7
A	see abstract see page 1, line 1 - line 15 see page 5 no 40 see claims	10-12
A	JOURNAL OF CELLULAR BIOCHEMISTRY vol. SUPPL, no. 15G, April 1991, page 31 A. KAKIZUKA ET AL. 'MOLECULAR CLONING AND CHARACTERIZATION OF ABERRANT RETINOIC ACID RECEPTORS FROM A t(15;17) POSITIVE ACUTE PROMYELOCYTIC LEUKEMIA PATIENT' see abstract	5

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 179, no. 3, 30 September 1991, pages 1554 - 1561 G. GRAUPNER ET AL. '6i-SUBSTITUTED NAPHTHALENE-2-CARBOXYLIC ACID ANALOGS, A NEW CLASS OF RETINOIC ACID RECEPTOR SUBTYPE-SPECIFIC LIGANDS' see the whole document ---	1-11
X	THE BIOCHEMICAL JOURNAL vol. 272, no. 2, 1990, pages 391 - 397 M. CRETTAZ ET AL. 'LIGAND SPECIFICITIES OF RECOMBINANT RETINOIC ACID RECEPTORS RARalpha AND RARbeta' see the whole document ---	1-10, 12-13,15
X	CHEM. PHARM. BULL. vol. 34, no. 5, 1986, pages 2275 - 2278 H. KAGECHIKA ET AL. 'DIFFERENTIATION INDUCERS OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS HL-60' see the whole document ---	1,2,6,12
X	EP,A,0 170 105 (SUMIMOTO PHARMACEUTICALS CO. LTD.) 5 February 1986 see abstract see page 2, line 19 - page 3, line 21 see page 7, line 10 - page 9, line 4; claims; example 68; table 2 ---	1,2,6,12
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 173, no. 1, 1990, pages 339 - 345 A. ASTROM ET AL. 'RETINOIC ACID AND SYNTHETIC ANALOGS DIFFERENTIALLY ACTIVE RETINOIC ACID RECEPTOR DEPENDENT TRANSCRIPTION' see the whole document ---	1-8, 12-13,14
X	CANCER LETTERS vol. 57, no. 3, 24 May 1991, pages 223 - 227 J.R. FREY ET AL. 'ANTIPROLIFERATIVE ACTIVITY OF RETINOIDS, INTERFERON alpha AND THEIR COMBINATION IN FIVE HUMAN TRANSFORMED CELL LINES' see the whole document ---	1,2,6,12

-/--

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07064

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/07; A61K31/20; A61K31/19

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	CANCER RESEARCH vol. 51, 15 September 1991, pages 4804 - 4809 J.M. LEHMANN ET AL. 'IDENTIFICATION OF RETINOIDS WITH NUCLEAR RECEPTOR SUBTYPE-SELECTIVE ACTIVITIES' see the whole document ---	1-8
P,X	MOLECULAR PHARMACOLOGY vol. 40, no. 4, October 1991, pages 556 - 562 C. DELESCLUSE ET AL. 'SELECTIVE HIGH AFFINITY RETINOIC ACID RECEPTOR alha OR beta-gamma LIGANDS' see the whole document --- -/--	1-11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 OCTOBER 1992	24. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar [illegible]

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207064 SA 64154

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0170105	05-02-86	JP-A- 61022047	30-01-86
		JP-A- 61076440	18-04-86
		US-A- 4703110	27-10-87
EP-A-0220118	29-04-87	FR-A- 2590566	29-05-87
		FR-A- 2601359	15-01-88
		AU-B- 588385	14-09-89
		AU-A- 6385986	16-04-87
		CA-A- 1270766	26-06-90
		CA-A- 1267420	03-04-90
		DE-A- 3683240	13-02-92
		JP-A- 62135441	18-06-87
		US-A- 4826969	02-05-89

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

As the below-named inventors, we hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled USE OF SELECTIVE LIGANDS FOR TREATMENT OF HORMONE RESPONSIVE DISEASE STATES, the specification of which

_____ is attached hereto.

_____ was filed on August 21, 1992 as Application Serial No. PCT/US92/07064

and was amended on (or amended through) _____. (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
798,767	8/23/91	Pending
PCT/US92/07064	8/2/92	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

STEPHEN E. REITER, Registration No. 31,192; STEPHANIE L. SEIDMAN, Registration No. 33,779; JAMES R. BRUEGGEMANN, Registration No. 28,286; ROBERT A. SCHROEDER, Registration No. 25,393; LAURENCE H. PRETTY, Registration No. 25,312; and GARY A. CLARK, Registration No. 28,060.

Direct all telephone calls to:
STEPHEN E. REITER
Telephone: (619) 546-4737

Address all correspondence to:

STEPHEN E. REITER
Pretty, Schroeder, Brueggemann & Clark
444 South Flower Street, Suite 2000
Los Angeles, California 90071

Full name of first inventor: RONALD M. EVANS

Inventor's signature: Ronald M Evans

Date: Jan 26, 1994

Residence: La Jolla, California

Citizenship: United States

Post Office Address: 8615 La Jolla Scenic Road North
La Jolla, California 92037

Full name of second inventor: RICHARD A. HEYMAN

Inventor's signature: _____

Date: _____

Residence: Encinitas, California

Citizenship: United States

Post Office Address: 147 Honeycomb Court
Encinitas, California 92024

Full name of third inventor: CHRISTINA S. BERGER

Inventor's signature: _____

Date: _____

Residence: San Diego, California

Citizenship: United States

Post Office Address: 4256 Caminito Terviso
San Diego, California 92122

Full name of fourth inventor: ROBERT B. STEIN

Inventor's signature: _____

Date: _____

Residence: San Diego, California

Citizenship: United States

Post Office Address: 4431 Heritage Glen
San Diego, California 92130

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

As the below-named inventors, we hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled USE OF SELECTIVE LIGANDS FOR TREATMENT OF HORMONE RESPONSIVE DISEASE STATES, the specification of which

_____ is attached hereto.

_____ was filed on August 21, 1992 as Application Serial No. PCT/US92/07064 and was amended on (or amended through) _____. (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
798,767	8/23/91	Pending
PCT/US92/07064	8/2/92	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

STEPHEN E. REITER, Registration No. 31,192; STEPHANIE L. SEIDMAN, Registration No. 33,779; JAMES R. BRUEGGEMANN, Registration No. 28,286; ROBERT A. SCHROEDER, Registration No. 25,393; LAURENCE H. PRETTY, Registration No. 25,312; and GARY A. CLARK, Registration No. 28,060.

Direct all telephone calls to:
STEPHEN E. REITER
Telephone: (619) 546-4737

Address all correspondence to:

STEPHEN E. REITER
Pretty, Schroeder, Brueggemann & Clark
444 South Flower Street, Suite 2000
Los Angeles, California 90071

Full name of first inventor: RONALD M. EVANS

Inventor's signature: ______________________

Date: ______________________

Residence: La Jolla, California

Citizenship: United States

Post Office Address: 8615 La Jolla Scenic Road North
La Jolla, California 92037

Full name of second inventor: RICHARD A. HEYMAN

Inventor's signature: Richard A. Heyman

Date: 1/3/94

Residence: Encinitas, California

Citizenship: United States

Post Office Address: 147 Honeycomb Court
Encinitas, California 92024

Full name of third inventor: CHRISTINA S. BERGER

Inventor's signature: Christina S. Berger

Date: 2/4/94

Residence: San Diego, California

Citizenship: United States

Post Office Address: 4256 Caminito Terviso
San Diego, California 92122

Full name of fourth inventor: ROBERT B. STEIN

Inventor's signature: Robert B. Stein

Date: 1/28/94

Residence: San Diego, California

Citizenship: United States

Post Office Address: 4431 Heritage Glen
San Diego, California 92130